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The essential predictors of recurrence in patients with hepatocellular carcinoma after liver transplantation

Recurrence of hepatocellular carcinoma after liver transplantation

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Abstract
Aim: Liver transplantation is the optimal treatment for a selected group of patients with hepatocellular carcinoma (HCC). Post-transplant recurrence is common and markedly reduces the long-term survival of patients with HCC. The present study focuses on determining the predictive factors affecting the recurrence of HCC. Materials and Methods: Data of 106 patients with HCC who underwent liver transplantation between May 2012 and June 2018 were collected retrospectively. Variables were as follows: age, gender, preoperative alpha-fetoprotein (AFP) levels, MELD score, number of tumors, total tumor size and histological features. Results: Recurrence-free survival and overall survival rates were 91.5% and 94.3%, respectively. Cox regression analysis demonstrated that age, gender, MELD score, and Milan criteria had no effect on recurrence. Microvascular invasion (MVI) was detected in 55 patients (52%), and 51 patients (48%) had no MVI. The presence of MVI had a negative effect on tumor recurrence, and there was a statistically significant difference ($p<0.001$). There was also a significant difference in tumor recurrence between patients who had AFP levels under 400 IU/mL and those who had AFP levels above 400 IU/mL ($p<0.001$). Discussion: AFP level and the presence of MVI are significantly useful for predicting recurrence-free survival in patients with HCC following liver transplantation.

Keywords
Liver Transplantation; Hepatocellular Carcinoma; Recurrence

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Introduction

Liver transplantation (LT) is a forceful treatment and potential cure for hepatocellular carcinoma (HCC). Criteria based on the size and number of tumors are widely used for selecting HCC patients for LT. The recurrence of HCC remains the most important issue in this matter, affecting up to 20% of patients, despite the restrictive selection criteria [1].

Tumor size, histological findings, and preoperative alpha-fetoprotein (AFP) levels are currently the most important predictors for HCC recurrence in patients after LT [2,3], to the point that some reports argue that the combination of positron emission tomography (PET) positivity and AFP levels predict the recurrence risk better than tumor and number size do. These studies utilized preoperative PET results to define the histological features of the tumors [4,5].

In this retrospective study, we report a clinicopathological analysis of the risk factors affecting HCC recurrence after LT in a single center.

Materials and Methods

The design of this study was retrospective in nature. The approval of the local ethics committee was obtained with the protocol number 2018-17/4. We performed 514 LTs between May 2012 and June 2018 at our institution; 106 of these LTs were conducted on patients with HCC. The patients were reviewed on a retrospective basis, and the characteristics and outcomes of the patients were recorded. The factors affecting recurrence were evaluated.

Our selection criteria for HCC patients were mainly based on the Milan criteria, with patients selected if they demonstrated no evidence of extrahepatic metastases or macrovascular invasion. Computerized tomography angiography (CT-a) and magnetic resonance angiography (MR-a) were used to evaluate tumor size, tumor number, and any vascular invasions. PET imaging has been established as a diagnostic tool for evaluating metastatic liver tumors. Patients with AFP levels over 400 IU/mL were not accepted for LT. These patients underwent locoregional therapies (LRT), e.g. transarterial chemoembolization. If their AFP levels decreased below 400 IU/mL and did not increase above 400 IU/mL after the observation period following LRT, they were accepted for LT. Patients with a minimum one-year follow-up time and/or those who reached the end-point (recurrence and/or death) were enrolled in the study.

Statistical Analysis

Descriptive statistics were stated as percentages for categorical variables, and mean ± standard deviation or median and range were used for continuous variables. Comparisons were analyzed using the Chi-square test for categorical variables and the Student's t-test for continuous variables (if normality was observed) or Cox regression analysis (in other cases). Overall survival and tumor-free survival rates were estimated using the Kaplan-Meier method. A p-value of $p<0.05$ was considered statistically significant in all analyses.

Results

The baseline clinical characteristics of the 106 patients included in the study are summarised in Table 1. HCC recurrence was detected in nine patients, and six patients were lost due to HCC recurrence or other factors, e.g. biliary complications. Hence, during the minimum one-year follow-up period, recurrence-free survival and overall survival rates were 91.5% and 94.3%, respectively.

Age, gender, and MELD scores had no effect on recurrence. The recurrence rate was similar in patients within and beyond the Milan criteria. According to Cox regression analysis of tumor characteristics, number, size, total volume and histologic differentiation of tumors showed no significant effect on the recurrence of HCC.

Microvascular invasion (MVI) was detected in 55 patients (52%), and 51 patients (48%) had no MVI. The presence of MVI had a

Table 1. The clinical features of the patients

Gender (Male/Female)	93/13 (87.7% / 12.3%)
Age	57.1±8.2
MELD score	12.8±5.6
Milan criteria (in/out)	58/48 (54.7% / 45.3%)
Etiology	
Hepatitis B virus	62 (%58,4)
Hepatitis C virus	17 (%16)
Cryptogenic	13 (%12,2)
Alcoholic	5 (%4,7)
Budd-Chiari syndrome	2 (%1,8)
Hepatitis B and C virus	2 (%1,8)
Wilson disease	1 (%0,9)
HCC (non- cirrhotic)	4 (%3,7
AFP level	12.4 IU/mL (0.7 – 158)
Milan Criteria: in / out	58 (54.7%) / 48 (45.3%)

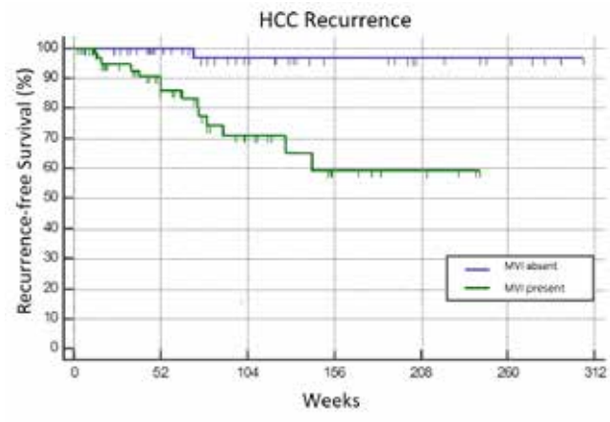

Figure 1. The association between microvascular invasion and recurrence

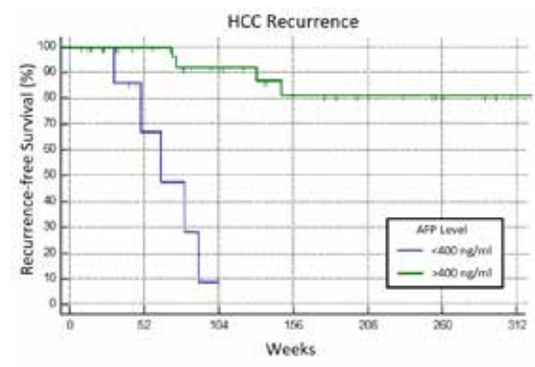

Figure 2. The association between AFP level and recurrence

negative effect on tumor recurrence, and there was a statistically significant difference (Figure 1, p<0.001). There was also a significant difference in tumor recurrence between patients who had AFP levels under 400 IU/mL and those whose AFP levels were above 400 IU/mL (Figure 2, p<0.001).

Discussion

In this retrospective study, univariate analysis of features of patients and tumors showed that AFP levels and the presence of MVI predicted recurrent rates of HCC in patients who underwent LT, independently of tumor size, number, grade and other clinical prognostic criteria like the Milan criteria. The recurrence rate was 8.5% in the present study, which is similar to that in the literature [6,7].

Morphological features, such as tumor numbers, diameter, total size, and total volume are mostly used as prognostic criteria. However, there is an increasing concern that strict criteria based on morphological features may exclude a significant number of patients from LT [8]. For this reason, expanded criteria have been developed in the last several decades, and substantial outcomes have been achieved [9,10,11]. We also used the Milan criteria to select patients for LT, and analysis of outcomes for our patients demonstrated no significant difference associated with post-LT recurrence of HCC.

AFP is commonly used as a prognostic factor and a monitoring tool for post-transplant recurrence [12]. Further, the reduction of AFP following LRTs is considered to be a positive prognostic factor. However, there is no consensus about a cut-off point in preoperative AFP [13,14]. We accepted patients with AFP levels of 400 IU/mL for LT; AFP levels over 400 IU/mL in patients were strongly associated with tumor recurrence.

MVI has also been determined to be an important predictive factor for recurrence in some studies [1,15]. Our results, in contrast, demonstrated that MVI is a poor diagnostic factor for recurrence. However, MVI is a histopathological diagnosis, and information about MVI cannot be obtained preoperatively. Only limited studies recommended using 18F-fluorodeoxyglucose PET to predict tumor differentiation and the presence of MVI [5,16]. We routinely used PET to evaluate the metastases of HCC. However, our data did not support the role of PET in determining MVI preoperatively.

Conclusion

This study demonstrated that MVI and AFP levels are the most valuable prognostic factors for predicting tumor recurrence. Early identification of predictive parameters for recurrence and a careful strategy for selection should be mandatory for patients with HCC who are to undergo LT.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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